PLAC™ TEST
Catalog Number: 90101

Enzyme Immunoassay for the Quantitative Determination of Lp-PLA2 in Human Plasma

FOR *IN VITRO* DIAGNOSTIC USE

STORE ALL TEST COMPONENTS AT 2 TO 8°C EXCEPT FOR THE CALIBRATORS. CALIBRATORS SHOULD BE STORED FROZEN (-20°C OR BELOW)

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INTENDED USE

The diaDexus PLAC™ test is an enzyme immunoassay for the quantitative determination of Lp-PLA2 (lipoprotein-associated phospholipase A2) in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease.

SUMMARY AND EXPLANATION

Lp-PLA2 is a calcium-independent serine lipase that is associated with low-density lipoprotein (LDL) in human plasma [1] and is distinct from other phospholipases such as cPLA2 and sPLA2 [2]. Lp-PLA2 is produced by macrophages and is expressed in greater concentrations in atherosclerotic lesions [3]. Several lines of evidence suggest that oxidation of LDL plays a critical step in the development and progression of atherosclerosis [4,5]. Lp-PLA2 participates in the oxidative modification of LDL by hydrolyzing oxidized phosphatidylcholines, generating lysophosphatidylcholine and oxidized free fatty acids, both of which are potent proinflammatory products that contribute to the formation of atherosclerotic plaques [6,7,8].

The diaDexus PLAC™ test is a sandwich enzyme immunoassay that uses two highly specific monoclonal antibodies for the direct measurement of Lp-PLA2 concentration in human plasma [9]. Elevated levels of Lp-PLA2, as measured by immunoassay, were found in patients with angiographically proven coronary heart disease, when compared to age matched controls [1]. Gender-specific clinical studies regarding the association of Lp-PLA2 and the risk of cardiovascular events have been limited [10, 11], warranting additional research in this area. In a retrospective case-control study, using samples from hypercholesterolemic men (n=6595) in the West of Scotland Coronary Prevention Study (WOSCOPS), a 2-fold greater risk of coronary heart disease was observed for subjects in the highest quintile of Lp-PLA2 levels, compared to the lowest quintile. Furthermore, the CHD risk association of Lp-PLA2 was shown to be independent of LDL and other markers of inflammation: C-reactive protein, white cell count and fibrinogen. The authors of the study stated in their Conclusions, "Elevated levels of lipoprotein-associated phospholipase A2 appear to be a strong risk factor for coronary heart disease, a finding that has implications for atherogenesis and the assessment of risk." [10].

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PRINCIPLE OF THE TEST

The diaDexus PLAC™ test is based on the principle of a sandwich enzyme immunoassay using two specific monoclonal antibodies described by Caslake *et al.* [1]. The assay system utilizes monoclonal anti-Lp-PLA2 antibody (2C10) directed against Lp-PLA2 for solid phase immobilization on the microtiter stripwells. The test sample is first diluted with the sample diluent and incubated at 2-8°C for 60 minutes. The diluted test sample is then allowed to react with the immobilized monoclonal antibody in the reaction well at 2-8°C for 90 minutes. The wells are washed with distilled water to remove any unbound antigen. A second monoclonal anti-Lp-PLA2 antibody (4B4) labeled with the enzyme horseradish peroxidase (HRP), is then added and reacted with the immobilized antigen at 2-8°C for 60 minutes, resulting in the Lp-PLA2 molecules being captured between the solid phase and the enzyme-labeled antibodies. The wells are washed with distilled water to remove unbound labeled antibodies. The substrate, tetramethylbenzidine (TMB) is then added and incubated at 2-8°C for 20 minutes resulting in the development of a blue color. Color development is stopped with the addition of Stop Solution, changing the color to yellow. The absorbance of the enzymatic turnover of the substrate is determined spectrophotometrically at 450 nm and is directly proportional to the concentration of Lp-PLA2 present. A set of Lp-PLA2 Calibrators is used to plot a standard curve of absorbance versus Lp-PLA2 concentration from which the Lp-PLA2 concentration in the test sample can be determined.

REAGENTS AND MATERIALS

Materials supplied with the kit:
(Sufficient for 96 wells)

- **Antibody Coated Strips** — **12 each**
  Mouse monoclonal anti-Lp-PLA2 (2C10) antibody coated microtiter stripwells
- **Calibrators 1-6** — **1 set, Lyophilized**
  (0, 10, 25, 50, 100 and 200 ng/mL)
  diaDexus recombinant Lp-PLA2 antigen (DDX-RA) in a protein stabilizing diluent (fetal calf serum)
- **Reconstitution Buffer** — **4 mL, Blue color**
  Buffered reagent
- **Sample Diluent** — **23 mL, Green color**
  Buffered reagent with bovine serum albumin
- **Assay Buffer** — **23 mL, Colorless**
  Buffered reagent with bovine serum albumin and mouse serum
- **Conjugate** — **23 mL, Red color**
  Mouse monoclonal anti-Lp-PLA2 (4B4) antibody conjugated to horseradish peroxidase in a buffered reagent with carrier proteins (fetal calf serum and mouse IgG)
- **TMB Reagent** — **11 mL**
  3,3',5,5'-tetramethylbenzidine in a mildly acidic buffer
- **Stop Solution** — **11 mL**
  1N HCl

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Materials required but not provided:

- Precision single and multi-channel pipettors: 0.02, 0.10, 0.20 and 0.5 mL
- Disposable pipette tips (A new pipette tip must be used for each addition of different samples or reagents during the assay procedure.)
- Vials and micro-tubes for storage of the reconstituted, aliquoted Calibrators and for dilution of test samples
- Distilled water
- Vortex mixer or equivalent
- Absorbent paper or paper towel
- A microtiter plate reader with a bandwidth of 10 nm or less and an optical density (O.D.) range of 3 or greater at 450 nm
- Computer software capable of point-to-point curve fit for calculating concentration of analyte from optical density (Optional)
- Ice and ice bucket
- PLAC™ test Controls (available separately, Catalog Number 90102)
- Plate sealers
- Graph paper for manual data reduction (optional)

WARNINGS AND PRECAUTIONS

- For *In Vitro* Diagnostic Use.
- All plasma samples should be treated as potentially biohazardous material.
- TMB reagent contains 3,3',5,5'-tetramethylbenzidine (TMB). If exposed on skin, immediately flush area with soap and water. If eyes are exposed, flush with copious amounts of water and seek immediate medical attention.
- Stop Solution contains 1N HCl. If exposed on skin, immediately flush area with soap and water. If eyes are exposed, flush with copious amounts of water and seek immediate medical attention.
- Test kits and reagents should be disposed in a manner consistent with relevant regulations.
- Do not use reagents past their expiration dates.
- Do not mix components from other lots of diaDexus PLAC™ test kits.
- Controls are not provided with the kit but can be purchased separately. It is recommended that the "high" and "low" controls be included in each patient run. If control values are not within acceptance limits, the assay should be repeated. Additional quality control testing may be necessary according to state and local requirements.

REAGENT PREPARATION AND STORAGE

1. Prior to running the assay, bring each Calibrator vial to room temperature (20-25°C) for 5 minutes and reconstitute each vial with 0.5 mL of Reconstitution Buffer within 2 minutes. Place the reconstituted vials on ice immediately. Allow the vials to stand on ice for 20 minutes with occasional mixing every 5 minutes.

2. Test kits should be stored at 2-8°C upon receipt, with the exception of the Calibrators. Store unreconstituted Calibrators frozen (at or below -20°C).

3. Components from opened kits may be used for up to one month if stored properly. If the Calibrators are intended to be reused, the reconstituted Calibrators should be aliquoted and frozen (-20°C or below) immediately after the 20 minute incubation in Reconstitution Buffer. Each aliquoted Calibrator should be frozen and thawed only once. All other kit components must be stored at 2-8°C. The microtiter stripwells should be kept sealed in the foil pouch with desiccant to minimize exposure to moisture.

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SPECIMEN COLLECTION AND STORAGE

Blood samples should only be collected in EDTA-plasma collection tubes and prepared using a standard plasma separation procedure. Blood may be stored up to four hours at 2-8°C before processing. After processing, plasma must be tested within three days when stored at 2-8°C, or stored at or below -20°C for longer storage. When transporting samples, unprocessed blood samples should be shipped cool on ice packs while processed plasma should be shipped frozen on dry ice. Samples may be frozen and thawed up to six times without affecting the Lp-PLA2 quantitation.

ASSAY PROCEDURE

Preparatory Steps

1. **It is recommended that Calibrators, controls, and patient samples be assayed in duplicate. Prepare sufficient materials to accommodate the required number of samples.**
2. Allow plasma patient samples, Calibrators and controls to thaw at room temperature and place on ice as soon as thawed.
3. All other reagents should be stored at 2-8°C and used directly from the refrigerator.
4. Vortex the samples and controls to mix thoroughly. Avoid foaming. Prepare 1:10 dilutions of all samples and controls with Sample Diluent in microtubes or equivalent on ice (e.g. 20 µL sample + 180 µL Sample Diluent). Do not dilute the Calibrators. Vortex the diluted samples and controls to mix thoroughly. Avoid foaming.
5. Incubate the diluted samples for 60 minutes at 2-8°C.
6. Remove the stripwell frame and required number of coated microtiter strips from the foil pouch. It is recommended that each Calibrator and control be run in duplicate. Return any unused strips to the original foil pouch. Ensure that the foil pouch contains the desiccant and that the pouch is resealed completely.

Sample Incubation

1. Pipet 200 µL of Assay Buffer into the appropriate wells of the coated microtiter strip.
2. Pipet 20 µL of undiluted Calibrators, diluted samples, and diluted controls into the appropriate wells. It is recommended that Calibrators, controls and patient samples be run in duplicate. Use a calibrated pipette set at 20 µL and a new pipette tip for each Calibrator, control or sample. Pre-wet the pipette tip by pipetting up and down in the sample, Calibrator or control three times, aspirate 20 µL, wipe off the tip using the side of the tube and dispense volume into the well. Mix by pipetting up and down multiple (5-7) times.
3. Apply a plate sealer and gently swirl the plate on a flat surface for 15-20 seconds to ensure mixing.
4. Incubate the plate at 2-8°C for 90 minutes.
5. At the end of the incubation period, carefully remove then discard the plate sealer. Wash the microtiter wells five (5) times with 300 µL per well of distilled or deionized water. (DO NOT USE TAP WATER) inverting and tapping the wells after each addition of distilled or deionized water.
6. Blot the inverted plate on clean, dry absorbent paper or paper towel after the final wash. Immediately proceed to the next step. Do not allow the stripwells to dry.

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Conjugate Incubation

1. Pipet 200 µL of Conjugate into each well.
2. Apply a plate sealer and gently swirl the plate on a flat surface for 15-20 seconds to ensure mixing.
3. Incubate the plate at 2-8°C for 60 minutes.
4. Remove the TMB Reagent from the refrigerator and store at room temperature (20-25°C) during the last 15 minutes of incubation.
5. At the end of the incubation period, carefully remove then discard the plate sealer. Wash the microtiter wells five (5) times with 300 µL per well of distilled or deionized water. (DO NOT USE TAP WATER) inverting and tapping the wells after each addition of distilled or deionized water.
6. Blot the inverted plate on clean, dry absorbent paper or paper towel after the final wash. Immediately proceed to the next step. Do not allow the stripwells to dry.

Substrate Incubation

1. Pipet 100 µL of TMB Reagent into each well.
2. Gently swirl the plate on a flat surface for 10-15 seconds to ensure mixing.
3. Incubate the plate at 2-8°C for 20 minutes in the dark.
4. Stop the reaction by adding 100 µL of Stop Solution to each well.
5. Gently swirl the plate on a flat surface for 20-30 seconds to ensure mixing. It is important to ensure that all of the blue color changes to yellow color completely.
6. Wipe moisture from the bottom of the plate using a paper towel.
7. Within 15 minutes of adding the Stop Solution, read the optical density at 450 nm using a microtiter plate reader.

PROCEDURAL NOTES

- Store all test reagents at 2-8°C. Except for the microtiter strips and TMB, do not bring reagents to room temperature prior to use.
- Do not reconstitute Calibrators until all the testing materials are diluted and ready for the assay.
- Always have the next step reagent ready two minutes before each washing step.
- A microtiter plate reader with a bandwidth of 10 nm or less and an optical density range of 3 O.D. or greater at 450 nm wavelength is acceptable for use in absorbance measurement.
- For accurate quantitation of sample concentrations of Lp-PLA2, Calibrators and controls must be precisely pipetted. Pipet carefully using only calibrated equipment.
- This assay may be performed using any validated washing method.

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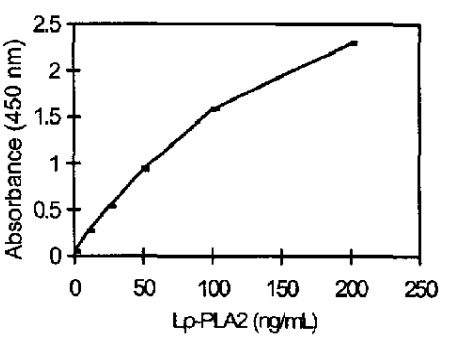
CALCULATION OF RESULTS

1. Examine the absorbance values (A_{450}) for each set of Calibrators, patient samples and controls that were run. If the average O.D. of the 200 ng/mL calibrator is less than 1.2, the assay should be repeated.
2. Construct a calibration curve by plotting the mean absorbance obtained for each Calibrator on the y-axis versus the Lp-PLA2 concentration in ng/mL on the x-axis, using a point-to-point curve fit with appropriate computer software. For manual data reduction, use graph paper to plot the mean absorbance obtained for each Calibrator on the y-axis versus the Lp-PLA2 concentration in ng/mL on the x-axis.
3. Using the mean absorbance value for each sample and control, interpolate the corresponding concentration of Lp-PLA2 in ng/mL from the calibration curve.
4. Results for the samples and controls should be multiplied by the pre-dilution factor of 10, to generate the final concentration of Lp-PLA2 (ng/mL) in these samples.
5. Patient samples with Lp-PLA2 concentrations greater than 2,000 ng/mL should be further diluted 10-fold with sample diluent after the initial 10-fold dilution (total dilution 1:100). Repeat the assay with the 1:100 diluted patient samples. Note that the measured Lp-PLA2 results should be multiplied by 100 to give the final concentration of Lp-PLA2 (ng/mL) in these samples.

EXAMPLE OF TYPICAL CALIBRATION CURVE

Results of a typical calibration curve with O.D. readings at 450 nm are shown on the Y axis against Lp-PLA2 concentrations (ng/mL) shown on the X axis. This calibration curve is for the purpose of illustration only. A calibration curve should be generated by the user for each assay performed.

Lp-PLA2 (ng/mL)	Mean Absorbance (O.D. at 450 nm)
0	0.043
10	0.267
25	0.530
50	0.938
100	1.586
200	2.298



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LIMITATIONS

Procedure

- Reliable and reproducible results will be obtained when the assay procedure is carried out with a complete understanding of the package insert instructions and with adherence to good laboratory practice.
- The wash procedures are critical. Insufficient washing will result in poor precision and falsely elevated absorbance readings.
- As with any assay system employing mouse monoclonal antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) present in the sample that could cause falsely elevated or depressed values.

Clinical Interpretation

- Lp-PLA2 levels should be interpreted in conjunction with clinical findings and other diagnostic tests, specifically, LDL results.
- This test does not replace blood cholesterol tests or replace other traditional risk factors identified for coronary heart disease.

EXPECTED VALUES

Samples from apparently healthy males (n=251) and apparently healthy females (n=174), in the clinically relevant age range of 40-70 years, were evaluated with the diaDexus PLAC™ test. The reference population was represented by the following ethnic backgrounds: African-American n = 26, Caucasian n = 390, Hispanic n = 8, not specified n = 1.

Population	n	5th-95th Percentile (ng/mL Lp-PLA2)
Females	174	120-342
Males	251	131-376

The reference interval calculated from the samples (central 90%) was found to be 120-342 ng/mL for females and 131-376 ng/mL for males. These ranges are provided as guidelines only. Each laboratory should establish its own reference intervals. Guidance for establishing reference intervals may be found in NCCLS Standard C28-A2 ("*How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline - Second Edition*").

PERFORMANCE CHARACTERISTICS

Sensitivity

The minimum detection limit, as calculated by interpolation of the mean plus two standard deviations of 24 replicates of the 0 ng/mL Lp-PLA2 Calibrator is 1.2 ng/mL.

Assay Precision

Intra-assay and inter-assay variability were determined by testing three human plasma pools with Lp-PLA2 concentrations distributed throughout the calibration range of the assay. The three plasma pools were assayed, using a single lot of reagents, in duplicate, on two separate stripwells per day, for twenty days. The data are summarized below:

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Plasma Pool	Mean Concentration Lp-PLA2 (ng/mL)	Intra-assay % CV n=80	Inter-assay % CV n=20
1	109	6.6	8.6
2	336	5.3	8.9
3	649	4.9	8.4

Linearity

Four EDTA-plasma samples containing different levels of endogenous Lp-PLA2 were diluted with Sample Diluent and assayed (dilution range: 1:5 to 1:20). Percent recovery was determined as the observed value divided by the expected value, multiplied by 100. The average recovery, demonstrating linearity of diluted samples over a range of 133 to 1310 ng/mL Lp-PLA2, was 104%.

Dilution Linearity

Six EDTA-plasma samples with known high Lp-PLA2 levels were intermixed with six plasma samples with known low Lp-PLA2 levels. Percent recovery was determined as the measured value divided by the expected value, multiplied by 100. The average recovery, demonstrating linearity of the diluted samples over a range of 79 to 982 ng/mL Lp-PLA2, was 104%.

Antigen Recovery

Known amounts of recombinant Lp-PLA2 (80, 179 and 436 ng/mL) were added to 15 human plasma samples and to fetal bovine serum (control). Recovery was determined as the observed spiked concentration in the plasma samples, calculated as a percent of the observed control concentration (with no endogenous Lp-PLA2). Results demonstrated a mean antigen recovery from 97-119% across the assay range, with an overall mean recovery of 109%.

Interfering Substances

Five endogenous substances found in blood were evaluated for interference in the assay. Five individual plasma samples with Lp-PLA2 values ranging from 92 to 664 ng/mL were spiked with potential interferents endogenous to blood. No appreciable interference was observed at spiked levels of 500 mg/dL hemoglobin, 3000 mg/dL triglycerides, 500 mg/dL cholesterol, 20 mg/dL bilirubin and up to 6.2 g/dL albumin.

CLINICAL STUDY

To determine the efficacy of the diaDexus PLAC™ test as a predictor of risk for coronary heart disease (CHD), Lp-PLA2 levels were measured in 1348 banked EDTA-plasma samples from a large, multi-center, epidemiology study, the Atherosclerosis Risk In Communities (ARIC) Study, sponsored by the National Institutes of Health's, National Heart, Lung, and Blood Institute. Participants were followed for the development of CHD for up to nine years. Samples used for the PLAC™ test were from participants, age 47-69, free of CHD at the time of blood drawn. This is a case-cohort study where samples from all the CHD cases (608) were tested together with 740 appropriated matched participants without CHD at the time of censor (controls).*

Cox regression models were used to evaluate the association of Lp-PLA2 and CHD in a univariate analysis (Model 1), a univariate analysis adjusted for demographics (Model 2), and a multivariate model adjusted for demographics and other prognostics factors (Model 3). Using

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high and low cutpoints of Lp-PLA2, generated from the ARIC data set (420 and 310 ng/mL, the 67th and 33rd percentiles, respectively), the hazard ratios of the Cox regression analyses demonstrated that Lp-PLA2 is a significant predictor of risk for CHD, for the highest and intermediate levels when compared to the lowest level of Lp-PLA2, for all participants (see Table 1). It should be noted that different cutpoints may be appropriate for different clinical populations.

** NOTE: 86 results (5.5%) were outside the assay acceptance criteria and were excluded from data analyses.*

Table 1. Risk Ratios of CHD for Subjects Across All LDL Levels

	Lp-PLA2 Risk Ratio (95% CI, p value)*		
Lp-PLA2 (ng/mL)	**<310**	**310-420**	**>420**
Model 1	**1.0**	**1.49** (1.11-1.99, p=0.008)	**2.50** (1.89-3.31, p<0.001)
Model 2	**1.0**	**1.24** (0.92-1.66, p=0.154)	**1.76** (1.32=2.36, p<0.001)
Model 3	**1.0**	**1.71** (1.06-2.75, p=0.029)	**2.12** (1.29-3.48, p=0.003)

*The lowest tertile with Lp-PLA2 values <310 ng/mL is used as the reference group

Model 1: univariate analysis
Model 2: adjusted for age, race, gender
Model 3: adjusted for age, race, gender, current smoking status, blood pressure, diabetes, HDL, LDL, CRP and Lp-PLA2 - LDL interaction

A significant interaction was found between Lp-PLA2 and LDL. Therefore, it was appropriate to evaluate Lp-PLA2 risk ratios in the high and low LDL subgroups. The median value of LDL for the cohort population was 130 mg/dL. This defined the high and low LDL subgroups. Table 2 represents the univariate analysis of the risk ratios in the high and low LDL subgroups. The risk ratios are calculated from Cox regression employing weighted case-cohort method with Barlow adjustment, n=1348.

Table 2a. Risk Ratios of CHD for Subjects with LDL <130 mg/dL

	Lp-PLA2 Risk Ratio (95% CI)*		
Lp-PLA2 (ng/mL)†	**<310**	**310-420**	**>420**
Risk Ratio	**1.0**	**2.17** (1.41-3.36)	**3.52** (2.25-5.49)
#CHD cases/total subjects in category	51/215 **(23.7%)**	75/195 **(38.5%)**	77/163 **(47.2%)**

*The lowest tertile with Lp-PLA2 values of <310 ng/mL is used as the reference group
†Lp-PLA2 cutpoints based on the ARIC Study Population across all LDL levels

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Table 2b. Risk Ratios of CHD for Subjects with LDL ≥130 mg/dL

	Lp-PLA2 Risk Ratio (95% CI)*		
Lp-PLA2 (ng/mL)†	**<350**	**350-460**	**>460**
Risk Ratio	**3.15** (2.08 – 4.77)	**3.66** (2.43-5.51)	**5.10** (3.43-7.57)
#CHD cases/total subjects in category	110/234 **(47.0%)**	126/247 **(51.0%)**	169/294 **(57.5%)**

*The lowest tertile for LDL <130 subgroup, with Lp-PLA2 values <310 ng/mL is used as the reference group
†Lp-PLA2 cutpoints based on the ARIC Study population with LDL ≥130 mg/dL

In the high LDL subgroup, the risk ratio increased with higher Lp-PLA2 cutpoints. Therefore, for individuals with high LDL, a higher Lp-PLA2 cutpoint should be considered. Further research is warranted to evaluate the Lp-PLA2 - LDL interaction in the subgroup with high LDL. For the total population, Lp-PLA2 was a significant predictor of risk for CHD for the high and intermediate groups versus the low Lp-PLA2 (reference) group.

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This product is covered by U.S. Patent Nos. 5532152, 5605801, 5641669, 5656431, 5698403, 5847088, 5968818, 5981252, and 6177257. Additional patents pending.

PLAC™ *is a pending trademark of diaDexus, Inc.*

P/N 30010
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